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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/760,285	01/15/2001	Nicholas C. Nicolaides	MOR-0017	2664

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EXAMINER	
NGUYEN, DAVE TRONG	
ART UNIT	**PAPER NUMBER**
1632	

DATE MAILED: 10/22/2003

Please find below and/or attached an Office communication concerning this application or proceeding.

Offic Action Summary	Application No.	Applicant(s)	
	09/760,285	NICOLAIDES ET AL.	
	Examiner	Art Unit	
	Dave T Nguyen	1632	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133).
- Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *30 July 2003* .

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☐ Claim(s) *1 and 4-82* is/are pending in the application.

4a) Of the above claim(s) *14-22,25,26,30-67,69 and 71* is/are withdrawn from consideration.

5)☐ Claim(s) *72-82* is/are allowed.

6)☐ Claim(s) *1,4-13,23,24 and 27-29* is/are rejected.

7)☐ Claim(s) *68 and 70* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on *30 July 2003* is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)☐ The proposed drawing correction filed on _____ is: a)☐ approved b)☐ disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____ .

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

14)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).

a) ☐ The translation of the foreign language provisional application has been received.

15)☐ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449) Paper No(s) _____ .
4) ☐ Interview Summary (PTO-413) Paper No(s). _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: .

Claims 1 and 72 have been amended by the amendment dated July 30, 2003. It is noted that claim 22 has been withdrawn from the examination but has been erroneously typed in the previous office action.

Claims 14-21, 22, 25-26, 30-67, 69, 71 remain withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected claimed invention.

Elected claims 1, 4-13, 23-24, 27-29, 68, 70, 72-82 readable on the elected invention are pending for examination.

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless --

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

(e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1, 4-13 are rejected under 35 USC 102(b) as being anticipated by, on the alternative, under 35 USC 103 as being unpatentable over Hubbard (Mutation Res. 85/4, p. 264, 1981).

Hubbard teaches a method of administering a polycyclic dimethylanthracene to effect an increased mutagenicity in isolated hepatocytes. Given the method steps and materials disclosed in the Hubbard reference are identical to that of the claims, the method of Hubbard would necessarily exhibit the biological function intended for any known dimethylanthracene including the 9,10,dimethylanthracene.

Claims 1, 4-13 are rejected under 35 USC 103 as being unpatentable over LaVoie, Carcinogenesis, Vol. 6, pp. 1483-1488, 1985 taken with any of Krahn, Mutation Res., Vol. 46, 27-44, 1997, and Wigley, Int. J Cancer, 23, 691-696, 1979, Slaga, Cancer Res., Vol. 38, 1699-1704, 1978, and further in view of Hubbbard, Mutation Res., 1981.

LaVoie teaches a method of administering an suitable or effective amount of numerous methylated anthracenes, *e.g.*, 1-, 2-, 99-, 2,9- and 9,10-demethylanthracene 9, as a carbon source for inducing tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes in an organism, *S. typhimurium* TA 98 and TA100.

Given the method steps and materials disclosed in LaVoie are identical to that of the claims, the method of LaVoie would necessarily exhibit the biological function intended for the employed methylated anthracene.

LaVoie does not teach the method done in an *in vitro* or cultured animal cell such as hepatocytes and Chinises hamster cells. However, such methods of using an anthracene or any well known mutagen is well-established in the prior art, as evidenced by the full disclosures of the cited Machala, Krahn, Wigley, Slaga, and Hubbbard.

It would have been obvious for of ordinary skill in the art to as a matter of design choice or minor modifications to employ any known anthracene including those elected anthracenes as taught in LaVoie in any in vitro or cultured animal cell. One of ordinary skill in the art would have been motivated to do so because the prior art, as exemplified by Machala, Krahn, Wigley, Slaga, and Hubbbard, does teach *in vitro* assays of employing well-established mutagens to study or measure the effect of mutation and/or genetoxicity is convention and well-established in the prior art. One would have expected that 1,2-dimethylanthracene would have necessarily produce

at least the same effect as demonstrated for other closely related methylated anthracenes employed in LaVoie, particularly since LaVoie teaches that on the basis of his study, wherein a different dose of methylated anthracenes was employed, the tumor-innitiating activity of methylated anthracenes can be initiated on mouse skin and in *S. typhimurium.* Moreover, the tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes as shown in LaVoie would necessarily generates a hypermutable cell wherein the presence of methylated anthracenes would necessarily inhibit activities of a mismatch repair in the cell, particularly since LaVoie employs identical method steps and materials as embraced by the claims, and particularly since the as-filed specification teaches that any methylated anthracene as embraced and cited in the claims would exhibit the inhibitory activity against a mismatch repair gene in the cell.

Thus, the claimed invention as a whole, was *prima facie* obvious.

Applicant argues on page 25 that LaVoie teaches away from the use of an *in vitro* assay in an *in vitro* cell, however, that fact that a dimethyl anthracene does not have significant tumor initiating activity in mouse skin cells does not constitute as a teaching away element. In fact, LaVoie also reviews the art of employing methylated anthracenes as a mutagene and teaches that on the basis oh his study, wherein a different dose of methylated anthracenes was employed, the tumor-innitiating activity of methylated anthracenes can be initiated on mouse skin (Tables I and II, page 1485, column 2, p. 1487, column 1 bridging column 2.). As such, and give the fact that Hubbard teaches a method of administering a polycyclic dimethylanthracene to effect an increased mutagenicity in isolated hepatocytes, and that *in vitro* assays are convenient and would

help to increase sensitivity and reproducibility of the results, particularly since LaVoie teaches that a lowere dosage and only a single administration of the amount of anthracene is employed, one of ordinary skill in the art would have been motivated to employ an *in vitro* assay with an increased dosage or amount as employed in any of the other cited prior art so as to ensure and/or enhance the sensitivity and reproducibility of the results and conclusion shown in the primary references.

Claims 23-24, 27-29 are rejected under 35 USC 103(a) as being unpatentable over any of Hubbard or LaVoie, Carcinogenesis, Vol. 6, pp. 1483-1488, 1985, taken with any of Krahn, Wigley and Slaga, and further in view of Chakravarti *et al.* (PNAS, Vol. 92, pp. 10422-10426, 1995).

Hubbard teaches a method of administering a polycyclic dimethylanthracene to effect an increased mutagenicity in isolated hepatocytes. Given the method steps and materials disclosed in the Hubbard reference are identical to that of the claims, the method of Hubbard would necessarily exhibit the biological function intended for any known dimethylanthracene including the 9,10,dimethylanthracene.

LaVoie teaches a method of administering an suitable or effective amount of numerous methylated anthracenes, *e.g.*, 1-, 2-, 99-, 2,9- and 9,10-demethylanthracene 9, as a carbon source for inducing tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes in an organism, *S. typhimurium* TA 98 and TA100. LaVoie also reviews the art of employing

methylated anthracenes as a mutagene and teaches that on the basis oh his study, wherein a different dosc of methylated anthracenes was employed, the tumor-innitiating activity of methylated anthraccnes can be initiated on mouse skin (Tables I and II, page 1485, column 2, p. 1487, column 1 bridging column 2.

Given the method steps and materials disclosed in Hubbard or LaVoie are identical to that of the claims, the method of LaVoie would necessarily exhibit the biological function intended for the employed methylated anthracene.

LaVoie does not teach thc method done in an *in vitro* or cultured animal cell such as hepatocytes and Chinises hamster cells. However, such methods of using an anthracene or any well known mutagen is well-established in the prior art, as evidenced by the full disclosures of the cited Machala, Krahn, Wigley, Slaga, and Hubbbard.

It would have been obvious for of ordinary skill in the art to as a matter of design choice or minor modifications to employ any known anthracene including those elected anthracenes as taught in LaVoie in any in vitro or cultured animal cell. One of ordinary skill in the art would have been motivated to do so because the prior art, as exemplified by Machala, Krahn, Wigley, Slaga, and Hubbbard, does teach *in vitro* assays of employing well-established mutagens to study or measure the effect of mutation and/or genetoxicity is convention and well-established in the prior art. One would have expected that 1,2-dimethylanthracene would have necessarily produce at least thc same effect as demonstrated for other closely related methylated anthracenes employed in LaVoie, particularly since LaVoie teaches that on the basis of his study, wherein a different dose of methylated anthraccnes was employed, the tumor-innitiating activity of methylated anthracencs can be initiated on mouse skin and in *S. typhimurium.* Moreover, the

tumor-initiating activity, mutagenicity, and metabolism of methylated anthracenes as shown in LaVoie would necessarily generates a hypermutable cell wherein the presence of methylated anthracenes would necessarily inhibit activities of a mismatch repair in the cell, particularly since LaVoie employs identical method steps and materials as embraced by the claims, and particularly since the as-filed specification teaches that any methylated anthracene as embraced and cited in the claims would exhibit the inhibitory activity against a mismatch repair gene in the cell. As such, and give the fact that Hubbard teaches a method of administering a polycyclic dimethylanthracene to effect an increased mutagenicity in isolated hepatocytes, and that *in vitro* assays are convenient and would help to increase sensitivity and reproducibility of the results, particularly since LaVoie teaches that a lowere dosage and only a single administration of the amount of anthracene is employed, one of ordinary skill in the art would have been motivated to employ an *in vitro* assay with an increased dosage or amount as employed in any of the other cited prior art so as to ensure and/or enhance the sensitivity and reproducibility of the results and conclusion shown in the primary references.

With respect to the limitation of employing an assay to test whether or not a mutation has occurred in a gene of interest as the result of the effect of a chosen anthracene, wherein the limitation is not taught by either Hubbard or LaVoie, Chakravarti teaches that such assays are conventional and routine in the prior art to assay for the effect of gene expression in the presence of an anthracene chosen for the mutation assay, Chakrawati, page 10422, and page 10423.

Thus, it would have been obvious for one of ordinary skill in the art to employ a gene report assay to determine the sensitivity and reproducibility of results due to exposure of tested

cells to a chosen anthracene such as 9/10, dimethylanthracene. One of ordinary skill in the art would have been motivated to employ any gene reporter assay known in the prior art in the mutation analysis method employed in the combined cited references because Machala and Chakravarti do teach that such assays are conventional and routine in the prior art to assay for the effect of gene expression in the presence of an anthracene chosen for the mutation assay, and because such incorporation of reporter gene expression assays would enhance the sensitivity and reproducibility of results due to exposure of tested cells to a chosen anthracene such as 9/10, dimethylanthracene.

Thus, the claimed invention as a whole, was *prima facie* obvious.

Applicant's argument (pages 26-29) has been considered by the examiner but is moot in view of the new grounds of the rejection.

Claims 68 and 70 are objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Claims 72-82 are free of the prior art of record.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to examiner *Dave Nguyen* whose telephone number is **(703) 305-2024**.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, *Deborah Reynolds*, may be reached at **(703) 305-4051.**

Papers related to this application may be submitted to Group 1600 by facsimile transmission. Papers should be faxed to Group 1600 via the PTO Fax Center located in Crystal Mall 1. The faxing of such papers must conform with the notice published in the Official Gazette, 1096 OG 30 (November 15, 1989). The CM1 Fax Center number is **(703) 305-7401**.

Any inquiry of a general nature or relating to the status of this application should be directed to the *Group receptionist* whose telephone number is **(703) 308-0196**.

Dave Nguyen
Primary Examiner
Art Unit: 1632

DAVE T. NGUYEN
PRIMARY EXAMINER